Docket No. 58086-241892
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of: Farhad Parhami	Art Unit: 1633
Application No: 10/524,945	Examiner: M.G. Leavitt
Confirmation No: 3129	Atty. Docket No: 58086-241892
Filed: February 16, 2005	Customer No: 26694 PATENT TRADEMARK OFFICE
For: AGENTS AND METHODS FOR ENHANCING BONE FORMATION	

DECLARATION UNDER 37 CFR 1.132

I, Farhad PARHAMI, hereby declare the following, based on my own knowledge, information, and belief:

1. I am an inventor in the above-identified application.

2. I am a Professor of Medicine at the David Geffen School of Medicine of the University of California, Los Angeles. I hold the degree of Doctor of Philosophy in Experimental Pathology from the University of California, Los Angeles (UCLA). I am the author or coauthor of approximately 40 scientific publications.

3. I have read and understood the Office Action dated March 23, 2009, as well as the cited references, including US published patent application no. 2004/0176423 ("Paralkar") and Parish *et al.* (1995) *Lipids*, pp. 247-251 ("Parish").

4. It is my understanding that the Examiner cites Paralkar for its alleged disclosure that HMG-CoA reductase inhibitors such as certain statins, in combination with prostaglandin agonists, can induce osteoblastic differentiation of mammalian mesenchymal stem cells (MSCs); and that she cites Parish for its disclosure of oxysterols that act as HMG-CoA reductase inhibitors. It is also my understanding that, based on these references, the Examiner alleges that a skilled worker would have expected inhibitors of HMG-CoA reductase other than the mentioned statins to also induce osteogenic differentiation, and that because some oxysterols have been reported to have anti-HMG-CoA reductase activity, a skilled worker would have expected the oxysterols to induce osteogenic differentiation.

5. However, Paralkar does not demonstrate a causal relationship between the inhibition of HMG-CoA reductase and the induction of osteoblastic differentiation in MSCs, and to my knowledge, such a causal relationship had not been demonstrated by others in the field of stem cell biology. Therefore, based on my extensive experience in this field, it is my opinion that neither I, nor other skilled workers, could have predicted with a reasonable expectation of success, at the time the present application was filed, whether an agent which inhibits HMG-CoA reductase, for example an oxysterol, would induce, would have no effect, or would inhibit, osteoblastic differentiation in MSCs.

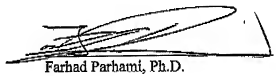
6. In fact, our research group published contemporaneously with the filing of the above-referenced patent application that the statin, metavastin, which inhibits HMG-CoA reductase, has the opposite effect of the statins described by Paralkar, and inhibits osteoblastic differentiation of MSCs, rather than stimulating it. Note that metavastin was one of the statins listed by Paralkar (*e.g.*, at paragraph [0011], line 9) as a statin that might be expected to stimulate bone formation; we showed that this is not the case. A copy of our paper - Parhami *et al.* (2002) *J. Bone & Mineral Res* 17, 1997 - is attached. Our observation confirms that there is not, in fact, a causal connection between the ability of an agent, such as the statins described by Paralkar, to inhibit HMG-CoA reductase and its ability to stimulate osteoblastic differentiation in MSCs.

7. Moreover, our research group has confirmed that the mechanism by which oxysterols induce osteoblastic differentiation is very different from the mechanism employed by the statins discussed by Paralkar. The osteogenic effect of the statins discussed by Paralkar is a result of BMP-2 expression. By contrast, the osteogenic effect of oxysterols is not a result of BMP-2 expression, but rather is mediated by aspects of the hedgehog signaling pathway.

8. In summary, to my knowledge, it was surprising and unpredictable at the time of the effective filing date of the above-referenced patent application that oxysterols would induce osteoblastic differentiation (and inhibit adipocyte differentiation) of MSCs. Neither I nor other researchers in the field of stem cell differentiation could have predicted this finding, with a reasonable expectation of success, on the basis of the Paralkar and Parish references, before the above-referenced patent application was filed.

9. I hereby declare that all statements made herein true, and that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Signed this 22 day of September, 2009



Farhad Parhami, Ph.D.

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